REMARKS

Claims 1, 3, and 5-82 are in this application. Claims 2 and 4 have been canceled. The subject matter of claim 2 except for lysine has been incorporated into claim 1. The subject matter of claim 4 except for lysine has been incorporated into claim 3. Claims 12 and 16 have been amended to delete reference to prevention. Claims 79 and 81 correspond to original claims 12 and 16 except they define prevention of the diseases and conditions. Claims 80 and 82 correspond to claims 13 and 17.

The Examiner has rejected claims 11, 32, 33 and 34 under 35 USC 112, first paragraph as not being enabled. Applicants respectfully traverse this rejection.

Although claims 11, 32, 33 and 34 have been canceled, these claims are enabled.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. United States v. Telectronics, Inc. 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). As explained below, one skilled in the art knows of the relationship between impaired glucose tolerance, insulin resistance and/or the effect of PPAR alpha and/or PPAR gamma on obesity, renal diseases, psoriasis, polycystic ovarian syndrome, leptin resistance and cancer. Based on this information and the disclosure in the specification it is clear that the claims which define compositions that are used to prevent and/or treat the diseases and conditions included in those claims are enabled.

Renal Diseases

Page 866 of the Chapter Endocrinology and Reproduction, Textbook of Medical Physiology, Eighth Edition, Arthur C. Guyton (W.B. Saunders Company).

In column 1 of this page it is stated "Because complications of diabetes-such as

atherosclerosis, greatly increased susceptibility to infection, diabetic retinopathy, cataracts, hypertension, and chronic renal disease-are more closely associated with the level of the blood lipids than with the level of blood glucose, it is the object of some clinics to administer sufficient glucose and insulin so that the quantity of blood lipids becomes normal." This reference teaches the relationship between blood lipids and renal diseases. Therefore, since the compounds of this invention reduce blood lipids, the treatment of renal diseases is enabled.

Ma, L.J. et al. Kidney Int. 2001 May; 59(5):1899-910 teaches that PPAR gamma beneficial effects are independent of insulin/glucose effects and are associated with regulation of glomerular cell proliferation... Therefore, since the compounds of this invention are ligands of PPAR gamma, the treatment of glomerular cell proliferation which is a renal disease is enabled.

Cancer

Pershadsingh, H. 131:317180, Expert. Opin. Invest. Drugs, 8(11), 1859-1872, 1999 describes that PPAR gamma agonists can promote apoptosis, block angiogenesis and inhibit pathol. remodelling in a variety of malignant and non-malignant pathol. states." This reference suggests that PPAR gamma agonists can be used for the treatment of cancer.

Kopelovich, L. Mol. Cancer. Ther. 2002 Mar; 1(5):357-63 discloses that activation of PPAR gamma and inhibition of PPAR delta may prevent cancer. "PPAR gamma agonists induce differentiation, inhibit the growth of established tumor cells in vitro and in vivo and have chemopreventive effects modies. PPARalpha has anti-inflammatory and differentiating activity and protects against the oxidative damage associated with aging. ...This review presents a rationale for using PPAR modulators as cancer chemopreventive drugs." Since the compounds of this invention are ligands of PPAR alpha and PPAR gamma, the treatment of cancer is enabled.

Dementia

Watson, G.S. et al. CNS Drugs 2003: 17(1):27-45 describes evidence that "suggests that an increased prevalence of insulin abnormalities and insulin resistance in Alzheimer's disease may contribute to the disease pathophysiology and clinical symptoms." The abstract also discloses that the insulin plays a role in memory functions. It is stated in the abstract that "The increased occurrence of insulin resistance in Alzheimer's disease and the numerous mechanisms through which insulin may affect clinical and pathological aspects of the disease suggest that improving insulin effectiveness may have therapeutic benefit for patients with Alzheimer's disease."

Claude Messier, et al. Behavioural Brain Research 75(1996):1-11. This paper discusses the relationship between Alzheimer's disease and glucose and concludes in the second column on page 7 "There are indications that treatment of altered glucoregulation in AD patients with anti-diabetic drugs could lead to small but significant improvements in cognitive function."

Therefore, since it has been shown that the compounds of this invention can be used to treat insulin resistance, the treatment of dementia is enabled.

Obesity

Michaela Modan, J. Clin. Invest. Vol. 75, March 1985, 809-817 discusses the relationship between impaired glucose tolerance and obesity.

Koutnikova H., Ann. N.Y. Acad. Sci. 2002 Jun.: 967:28-33 describes the relationship between PPAR gamma and obesity.

Therefore, since the compounds of this invention are ligands of PPARgamma, the treatment of obesity is enabled.

PCOS

Nestler, John E. 131:128241 Contemp. Endocrinol. 12:347-365, 1999 is the abstract of a review that reviewed 95 refs. and concluded that the evidence supports the pathogenic role of hyperinsulinemia in polycycstic ovary syndrome (PCOS). This abstract describes the correlation of hyperinsulinemia and PCOS.

Wyne, Kathleen, et al. 130:204564, Curr. Opin. Endocrinol. Diabetes, 5(4), 321-329, 1998 Lippincott Williams & Wilkins is the abstract of a review of 40 references. "This article reviews new developments in the field of polycystic ovarian syndrome and insulin resistance and focusing on the inter-relationship of the two syndromes.

Legro, R.S. 129:342122, Rev. Argent. Endocrinol. Metab. 35(1), 22-41, 1998 discloses that PCOS is associated with significant insulin resistance as well as with defects in insulin secretion. "The initial investigational use of insulin-sensitizing agents in these [PCOS] women has shown favorable response. Therefore, since it has been shown that the compounds of this invention, can be used to treat insulin resistance and impaired glucose tolerance, the treatment of PCOS is enabled.

This is also disclosed in Andrea Dunaif, Chapter 9, Insulin Resistance and Ovarian Dysfunction.

Therefore, since it has been shown that the compounds of this invention, can be used to treat insulin resistance and impaired glucose tolerance, the treatment of PCOS is enabled.

Psoriasis

Ellis, C.N. et al. Arch. Dermatol. 2000 May; 136(5):609-16 teaches that ligands for PPAR gamma inhibited the proliferation of normal and psoriatic human keratinocytes in culture. Since the compounds of this invention are ligands of PPAR , the treatment of psoriasis is enabled.

Leptin Resistance

In regard to leptin resistance, the examiner's attention is drawn to paragraph [00013] of this application.

Jens C. Bruning, et al. Science 2000;289:2122-2125.

According to page 2124 of this article, there is an interesting link between insulin and leptin action in the regulation of body weight.

Given this information and the information in the specification, the claims are in compliance with the enablement requirement and it is respectfully requested that the rejection be withdrawn.

Page 866 of the Chapter Endocrinology and Reproduction, Textbook of Medical Physiology, Eighth Edition, Arthur C. Guyton (W.B. Saunders Company).

In column 1 of this page it is stated "Because complications of diabetes-such as atherosclerosis, greatly increased susceptibility to infection, diabetic retinopathy, cataracts, hypertension, and chronic renal disease-are more closely associated with the level of the blood lipids than with the level of blood glucose, it is the object of some clinics to administer sufficient glucose and insulin so that the quantity of blood lipids becomes normal." This reference teaches the relationship between blood lipids and renal diseases. Therefore, since the compounds of this invention reduce blood lipids, the treatment of renal diseases is enabled.

Ellis, C.N. et al. Arch. Dermatol. 2000 May; 136(5):609-16 teaches that ligands for PPAR gamma inhibited the proliferation of normal and psoriatic human keratinocytes in culture. Since the compounds of this invention are ligands of PPARγ, the treatment of psoriasis is enabled.

Cancer

Pershadsingh, H. 131:317180, Expert. Opin. Invest. Drugs, 8(11), 1859-1872, 1999 describes that PPAR gamma agonists can promote apoptosis, block angiogenesis and inhibit pathol. remodelling in a variety of malignant and non-malignant pathol. states." This reference suggests that PPAR gamma agonists can be used for the treatment of cancer.

Kopelovich, L. Mol. Cancer. Ther. 2002 Mar; 1(5):357-63 discloses that activation of PPAR gamma and inhibition of PPAR delta may prevent cancer. "PPAR gamma agonists induce differentiation, inhibit the growth of established tumor cells in vitro and in vivo and have chemopreventive effects modies. PPARalpha has anti-inflammatory and differentiating activity and protects against the oxidative damage associated with aging. ...This review presents a rationale for using PPAR modulators as cancer chemopreventive drugs." Since the compounds of this invention are ligands of PPAR alpha and PPAR gamma, the treatment of cancer is enabled.

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numerous mechanisms through which insulin may affect clinical and pathological aspects of the disease suggest that improving insulin effectiveness may have therapeutic benefit for patients with Alzheimer's disease."

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Therefore, since it has been shown that the compounds of this invention can be used to treat insulin resistance, the treatment of dementia is enabled.

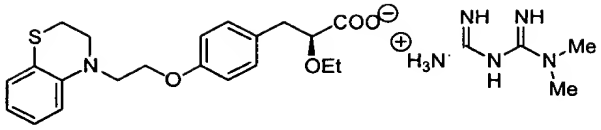
In view of the above, applicants submit that claims 11, 32, 33 and 34 are enabled and it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 1, 2, 7-11 and 27-34 under 35 USC 112, second paragraph. Applicants respectfully traverse this rejection.

Claim 1 has been amended to define a pharmaceutically acceptable salt. Claim 11 has been cancelled. However, the Examiner's comments will be taken into account when the claims of Group III are rejoined.

The Examiner has rejected claims 1, 8-11 and 29 under 35 USC 102(b) as being anticipated by Lohray et a. WO 99/20614. Applicants respectfully traverse this rejection.

In response to the species requirement, the compound of example 2 was identified. The species of example 2 is not the same as the compound of example 30 of WO 99/20614. The stereochemistry of example 30 of the PCT publication no. WO 99/20614 is not defined. Example 30 provides for the possibility of a mixture of two isomers. The compound of example 2 defines the specific isomer.



Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). Therefore, since there is a difference between the compound of example 30 and the subject matter of claims 1, 8-11 and 29, the rejection must be withdrawn.

In addition, the following data supports the applicant's statement that compound 30 does not anticipate these claims.

Compound	Fold activation of PPARα at 50μM	Fold activation of PPARγ at 1 μM
Example 30	5	13
Example 2	3	9.8

Compound	Dose (mg/kg)	Reduction in blood glucose level (%)	Triglyceride lowering (%)
Example 30	0.3	55	57
Example 2	0.03	56	59

Hyperlipidemic effect in Swiss Albino Mice

Compound	Dose (mg/kg)	Percent reduction of non-fasting triglyceride level
Example 30	0.3	67
Example 2	0.3	55

Furthermore, in claim 1 M is defined as N-methylglucamine, N-octylglucamine, dicyclohexylamine, methyl benzylamine, tris(hydroxymethyl)aminomethane, phenyl glycinol, aminoguanidine, aminoguanidine hydrogen carbonate or metformin. These salts are not disclosed in WO 99/20614.

Therefore, for all the reasons discussed above, claims 1, 8-11 and 29 are not anticipated by WO 99/20614.

It is respectfully requested that this rejection be withdrawn.

The Examiner rejected claims 1-2, 7-11, 27-34 and 78 under 35 USC 103(a) as being unpatentable over Lohray et al. WO 99/20614. Applicants respectfully traverse this rejection.

Claims 1 and 2 have been combined and M is defined as N-methylglucamine, N-octylglucamine, dicyclohexylamine, methyl benzylamine, tris(hydroxymethyl)aminomethane, phenyl glycinol, aminoguanidine, aminoguanidine hydrogen carbonate or metformin. None of these salts are disclosed or suggested by WO 99/20614. The Examiner is respectfully requested to refer to the list of salts on page 15, line 26-32 of WO 99/20614.

The standard test used to establish *prima facie* obviousness is the test set out by the Supreme Court in *Graham v. John Deere* (383 US 1, 148 USPQ 459 (1966)). To determine whether a claim is *prima facie* obvious:

1) the scope and content of the prior art are to be determined;

2) the differences between the prior art and the claims at issue are to be ascertained; and

3) the level of ordinary skill in the pertinent art resolved.

In addition, according to MPEP 2141, citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n. 5 (Fed. Cir. 1986), when applying 35 USC 103, the following tenets of patent law must be adhered to:

1) the claimed invention must be considered as a whole;

2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and

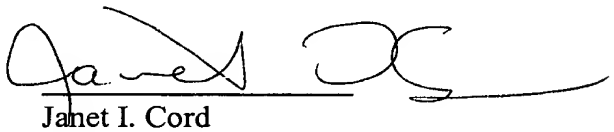
3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

Reasonable expectation of success is the standard with which obviousness is determined. *In re Merck & Co., Inc.*, 800 F.2d109, 231 USPQ 375 (Fed. Cir. 1986).

If one skilled in the art considers the claimed invention and WO 99/20614 as a whole, it is clear there is nothing in the reference which suggests the invention of claims 1-2, 7-11, 27-34 and 78.

Therefore, it is respectfully requested that the rejection be withdrawn.

Respectfully submitted,



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